IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Rein *et al.*

Serial No.: 09/980,727

Filed: July 8, 2002

For: METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED-RELEASE MATRIX

Confirmation No.: 8812

Art Unit: 1615

Examiner: Simon J. Oh

Attorney Docket No.: 11390-009

DECLARATION OF DR. HUBERT REIN UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Hubert Rein, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application.

2. I am currently Privatdozent at the University of Bonn.

3. My academic background and technical experience are set forth in my *curriculum vitae*, attached hereto as Exhibit 1.

4. I have reviewed the above-identified patent application, the pending claims, and the Office Action mailed January 11, 2006. I understand that the Examiner has rejected the claims under 35 U.S.C. § 103(a), on the allegation that International Publication No. WO 92/15285 to Lentz *et al.* ("Lentz") renders obvious the claimed methods and matricies produced thereby due to an alleged overlap in the temperature parameters.

5. I have reviewed the Lentz *et al.* patent publication. Lentz discloses compositions comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80 °C to 240 °C in a closed volume wherein the water content of the

matrix was maintained at about 5% to about 45% by weight based on the starch/water mix, and (ii) an active ingredient. Preferably, the starch is processed to a specific endothermic transition just prior to oxidation and thermal degradation. Note that the active ingredient is not processed with the starch but is merely combined with the starch after processing. See Lentz at page 11, lines 13-25; at page 14, lines 16-25. Moreover, the processed starch in Lentz, called molecularly dispersed starch or MDS, is not stiff or glassy, but, rather, is soft and rubbery, which allows the extruded MDS to be more compressible. See Lentz at page 28, lines 31-38, which teaches that the MDS obtained by extrusion is soft and rubbery. Even though both Lentz and the present invention teach destructurization of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lentz is soft and rubbery and, thus, <u>above</u> glass transition temperature. In fact, Lentz teaches at page 14, lines 6-25, that it is preferred that the process heats the starch above the glass transition temperature. In contrast, the extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains <u>below</u> the glass transition temperature. This structural difference between the starch matrices of the present invention and that of Lentz is a consequence of the differences in the disclosed methods, *inter alia*, wherein the temperature at the orifice of the extruder during the extrusion process is below 100 °C under normal pressure.

6. Importantly, the teaching of Lentz regarding the temperature range of 80 °C to 240 °C for processing does not mean that the processing can take place at any temperature between 80 °C to 240 °C but rather means that the entire process occurs at temperature encompassing 80 °C to 240 °C, never just at 80 °C or 130 °C or 240 °C. This is an important distinction as, contrary to the Examiner's assertion, there are no overlapping temperatures between the two processes. One skilled in the art of extrusion would clearly understand that Lentz is giving the range of the temperatures of the extruder, which temperatures differ at different locations of the extruder. Lentz specifically teaches on page 28, lines 17-19 that the extruder barrel temperature profile was 80 °C – 160 °C – 240 °C (for feed, screw and die, respectively). One skilled in the art would understand that the temperature of the extruder orifice (die) is 240 °C. This is an important distinction between the teachings of Lentz and the presently claimed invention, where the orifice of the extruder is below 100 °C, which also means that all other parts of the extruder are below 100 °C.

7. The only passage in Lentz that concerns co-extrusion of a pharmaceutically active agent and a starch is on page 17, line 37 to page 18, line 1. However, there are absolutely no details in the Lentz specification to teach one skilled in the art how such a co-extrusion can be carried out, unless the co-extrusion is carried out by the same methodology as Lentz uses to extruded the starch alone. Example 18 in Lentz, however, does provide details for a method of co-extrusion. However, Example 18 teaches co-extrusion of not starch but molecularly dispersed starch (which was previously extruded starch) with an active agent (clotrimazole) and talc. Further, as explicitly stated by Lentz, the resulting co-extruded product is a foamed, rubbery product, which is not a controlled release matrix. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix, *i.e.*, glassy. A foamed, rubbery product is not a glassy vitrified product.

8. Further, I have performed experiments and/or experiments have been performed under my supervision and direction demonstrating that using the process of Lentz (over 100 °C) only popped (foamed) products are produced, whereas using the process of the present invention (under 100 °C) a vitrified product is produced.

9. Attached as Exhibit 2 is a 30 page power point presentation entitled "Starch extrusion." This power point presentation details the experiments that were performed, namely comparing extrusion of a starch under the conditions taught in the present invention (DE 199 18 325 A1) and under the conditions taught in Lentz (WO 92/15285) using a Leistritz ZSE 27 HP 32 D extruder. On pages 4-6, results of extrusion of potato starch under the conditions of the present invention (at 80 °C) shows that the extrusion yielded a continuous strand of amorphous starch. However, raising the temperature to 114 °C resulted in popping-up of the exudates. Page 8 sets forth a summary of the products obtained at different die (extruder orifice) temperatures. Clearly, temperatures above 100 °C result in a popped product, not a vitrified product as required by the claims. In contrast, on age 12 the results of an extrusion process under the temperature conditions taught by Lentz using potato starch are shown. Basically nothing could be extruded as the extruder becomes completely blocked and the cylinder must be heated to above 300 °C in order to remove the starch (basically the starch had to be burned off). Pages 13 to 18 provide additional data demonstrating that temperatures above 100 °C lead to a popped-up product.

10. Page 20 of Exhibit 2 shows the design of four additional extrusion experiments and pages 21 to 28 show the results. Consistent with the above-data, when the

extrusion process takes place with temperatures under 100 °C a product of the claimed invention is produced. However, using temperature conditions taught in Lentz results in popped products that are not directly useable as a controlled-release dosage form. Page 29 concludes that the two different processes result in two different products.

11. Attached as Exhibit 3 is a power point slide setting forth additional evidence that extruding at high temperatures as taught by Lentz results in popped products. Further, Exhibit 4 is an Experimental Report summarizing the same experiments set forth on pages 20 to 28 of Exhibit 2.

12. In view of the foregoing, not only is the present invention nonobvious over Lentz due, for example, to the fact that there is no temperature overlap, but also the experimental evidence overwhelming shows that different products are produced using the two different methods.

13. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: 8.2.07

Hubert Rein

Dr.Hubert Rein
Eichenröder Weg 30

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»Curriculum vitae«

Date of birth:	2. September 1961 in Gießen/Lahn	
Marital status:	Married, one child	
Nationality:	German	
School attendance:	September 1968 - June 1981	Käthe-Kollwitz-Grundschule, Gießen Friedrich-Ebert-Gymnasium, Wieseck Liebig-Oberschule, Gießen
	June 1981	Abitur, Examination subjects: Physics, chemestry, german, History
National service:	July 1981 - September 1982	
University education:	April 1984 - October 1987	Study of pharmacy, Philipps-Universität Marburg an der Lahn, Degree: Pharmazeut
Training: (Pharmaziepraktikant):	October 1987 - April 1988	Dünsberg-Apotheke, 35444 Rodheim
	May 1988 - September 1989	ASTA Werke AG, 33647 Brackwede Pharm. quality control
Promotion:	September 1993	
Habilitation:	December 2003	
Appointments:	December 1989	Approbation as Apotheker
	February 1990 - December 1993	Member of the Direktorium of the Institute of Pharm. Technology, Philipps-Universität-Marburg
	October 1994	Akademischer Rat of the Pharmazeutische Technology, Universität Bonn
	October 1996	Official on lifetime
	October 1997	Member of the board of examiners of Pharmacy (Diplom), Universität Bonn
	January 2004	Privatdozent
Employments:	October 1982 - April 1984	Civil servant, Bundesanstalt für Arbeit (Federal employment office), Arbeitamt Gießen/Lahn

October 1988 - December 1989	Scientific assistant, Institut of Pharm. Technology, Philipps-Universität Marburg an der Lahn
January 1990 - December 1993	Scientific employee, Institut of Pharm. Technology, Universität Marbur an der Lahn
January 1994 - June 1994	Apotheker, Deutschhaus-Apotheke, Neukirchen/Schwalm
July 1994 - September 1994	Apotheker, Thomae GmbH Biberach an der Riß, R&D, department solid forms
Since October 1994	Rat (lecturer) of the Pharm. Technology, Bonn
October 1995 - December 1996	C3-Professor of Pharm. Technology, Technische Universität Braunscheig

Starch extrusion

PD Dr. Hubert Rein

Pharmaceutical technology

Bonn-Endenich

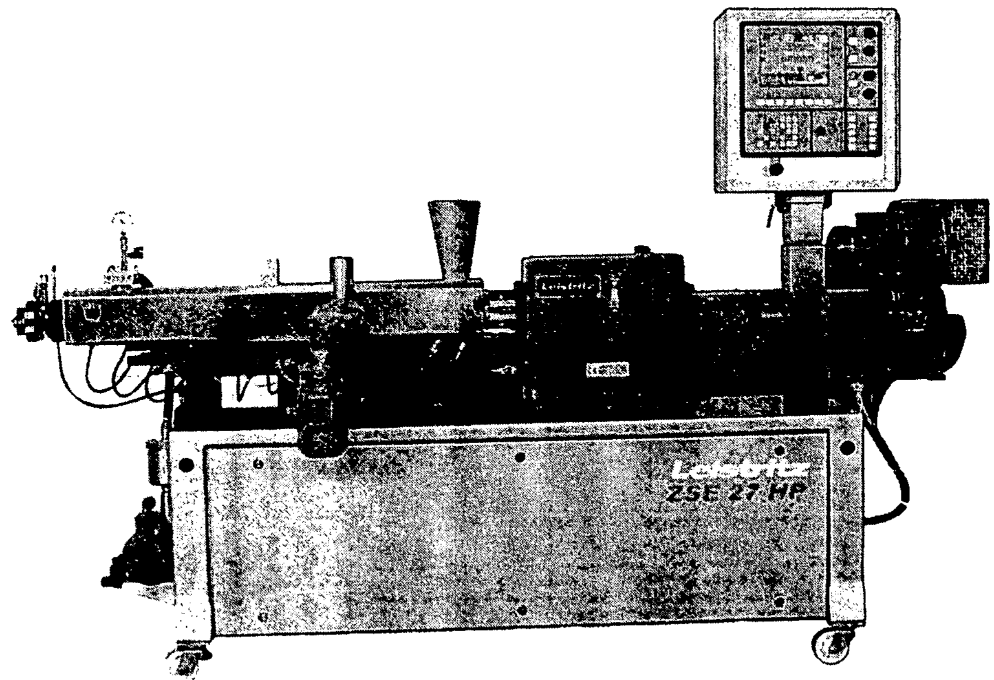
Starch extrusion: Overview

- Extrusion according to DE 199 18 325A1

  production of a mono block form (Extrudette)
  production of foamed extrudates (Xerogels)

- Extrusion according to WO 92/15285 and US 4,673,438

Extruder:



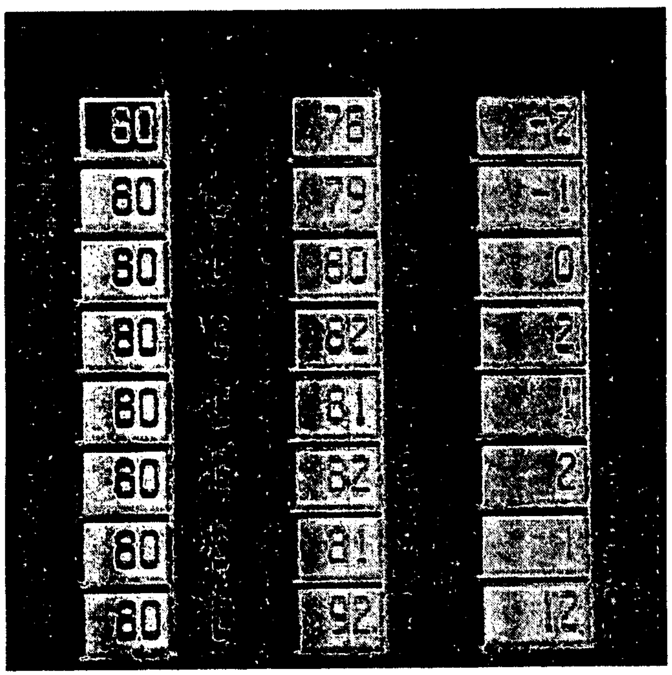
Leistritz ZSE 27 HP 32 D, Leistritz GmbH, Nürnberg

twin screw, co-rotating

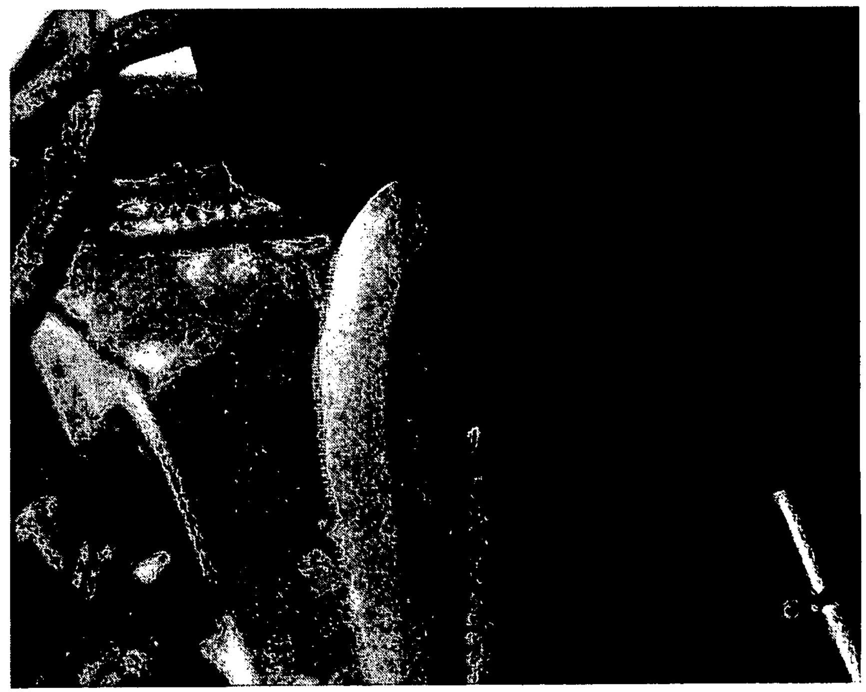
Extrusion according to DE 199 18 325A

round orifice: **5 mm**

temperaturE profil: **screw: 80 °C, Düse: 80 °C**



Temperature Display: ZSE 27



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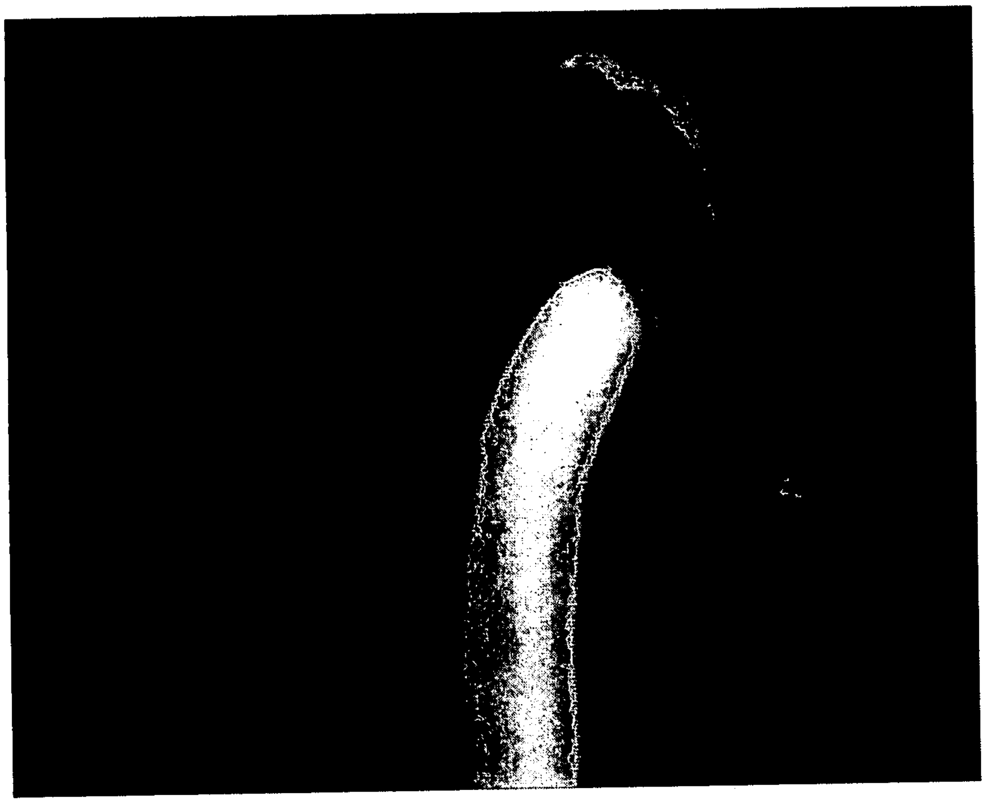
Extrusion according toDE 199 18 325A1 yields a continuous strand of amorphous starch.

Extrusion according to DE 199 18 325A1

Pelletisation of the extruded strand of amorphous strand is possible without encountering problems.



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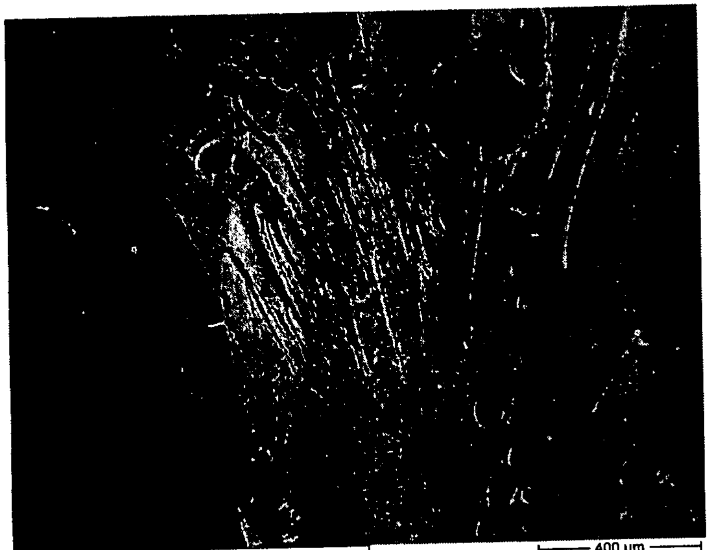
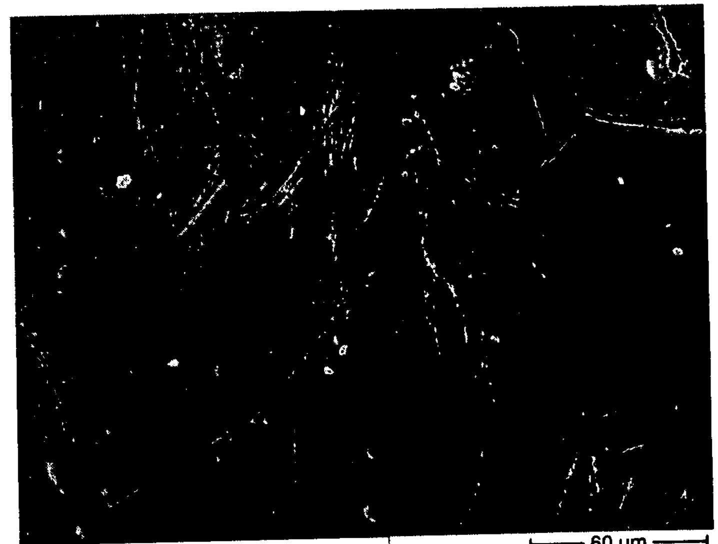
Example:
Hot cut with rotating knife

Pilot plant station of Leistritz GmbH Nürnberg

Extrusion according to DE 199 18 325A1



Potatoe starch extrudate, #250899D



Picture No. 1224, #240200M, released

Scanning electron microscopy pictures

left: fracture surface of an extrudate of amorphous starch

right: fracture through the extrudate after release of the dispersed active agent. The negative imprints of formerly incorporated active agent crystals (caffeine) are clearly visisble).

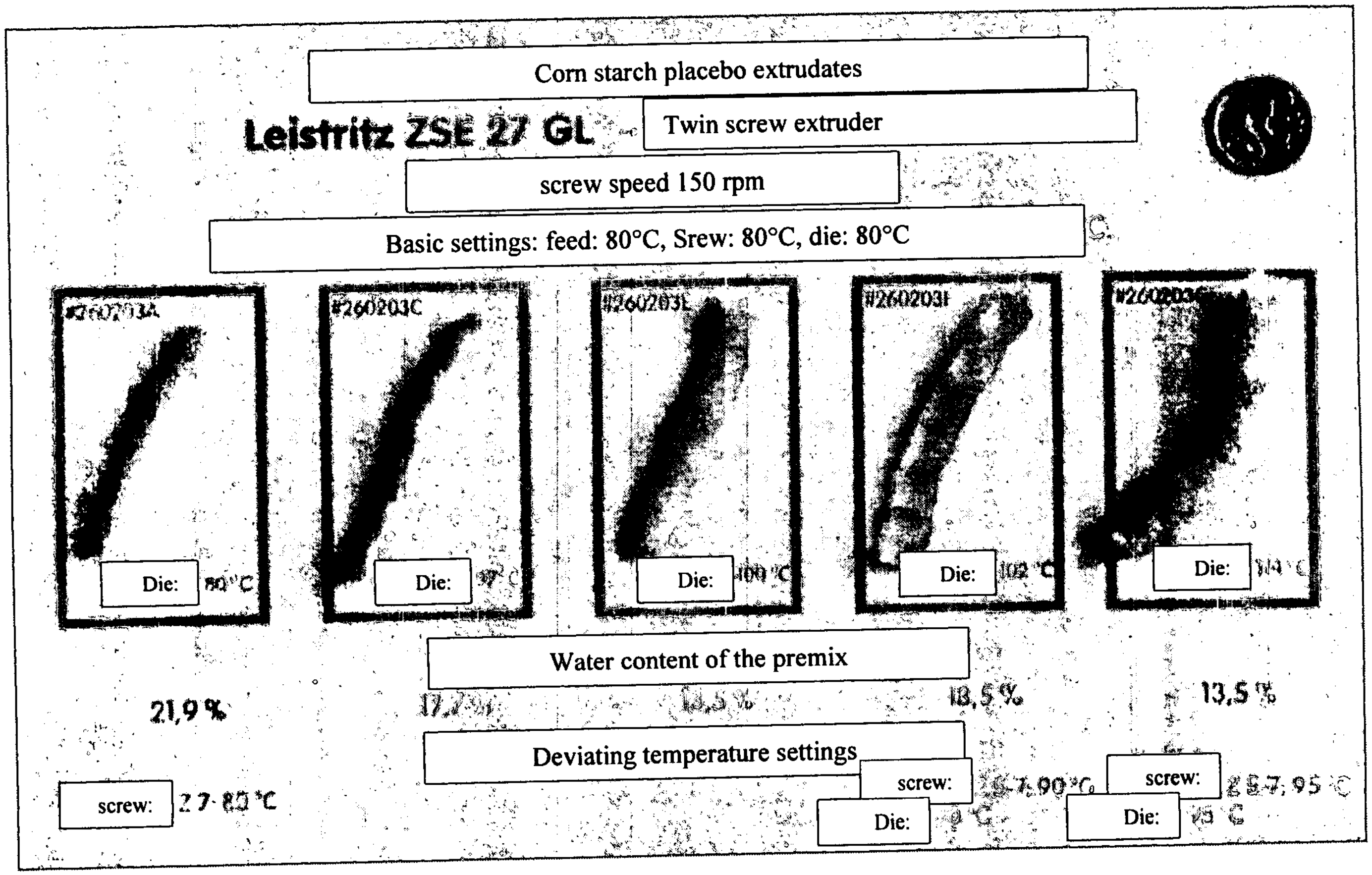
Extrusion according to DE 199 18 325A1

(click on black panl for starting)

A temperature increase of the die segment from 80°C to 114°C leads to popping up of the extrudate

Pilot plant station of
Leistritz GmbH Nürnberg

Extrusion according to DE 199 18 325A1



Product formation in dependence on temperature

Until 100 °C die temperature, one obtains a compact, cuttable extrudate. Higher temperatures lead to sudden evaporisation of the incorporated water and popping up of the extrudate strand when leaving the die. (Ch.B.: 260203G).

Extrusion according to DE 199 18 325A1

- Extrusion according to **DE 199 18 325A1** allows production of mono block dosage forms of amorphous starch.
- The active agent can be dispersed or dissolved within the amorphous starch.
- Extrusion according to **DE 199 18 325A1** allows for so called one-excipient concept.
- Extrusion proceeds such that water which is incorporated in the product does not evaporate upon leaving the die. The product is therefore

  a) free of bubbles and b) highly compact.

Stärkeextrusion nach US 4,673,438 und WO 92/15285

US 4,673,438 describes extrusion of potatoe starch (81 % potatoe starch, 19 % water, example 12) at a screw temperature of 110 to 130 °C and a die temperature of 130 °C.

As descrribed, one can not obtain a non-popped product at a product temperatue of about 130 °C and a water content of about 19%.

In WO 92/15285 more drastic conditions are used for extrusion: feed: 80 °C, screw 160 °C (Bsp. 11: 240 °C), die: 120 °C

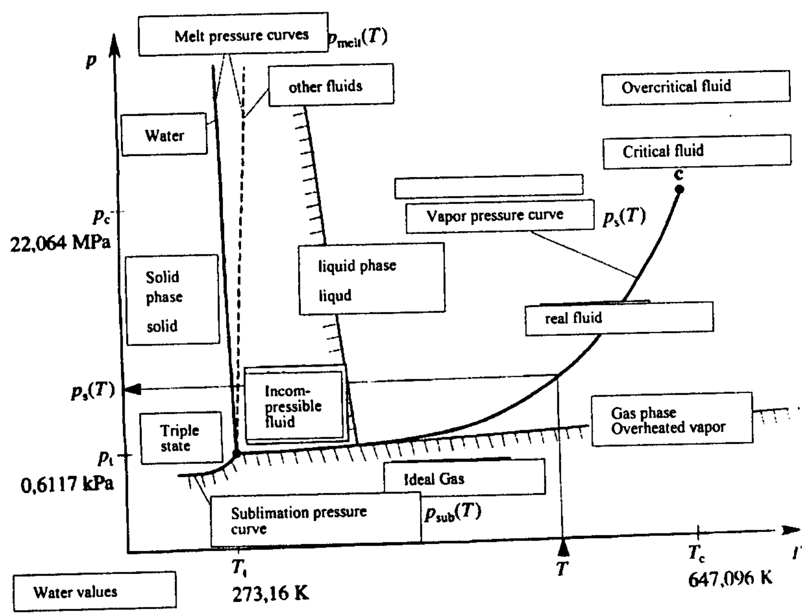
At a temperature of 80 °C in the feeding section, the starch agglutinates before enetering the extruder cylinder. Additionally, the extruder must be sealed towards ist rear end because if the high water vapor pressure in order to realise a screw temperature of 160°C in an aqueous surrounding.

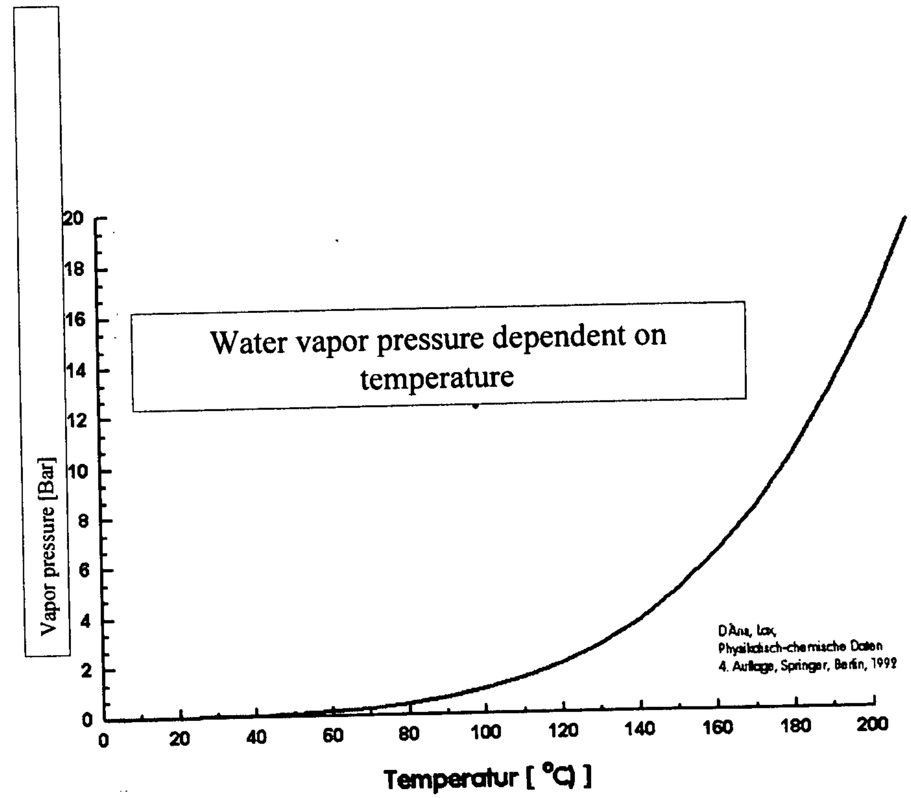
A controlled starch extrusion is not possible under these conditions.

See also following slide:

Phase diagram of water, vapor pressure development

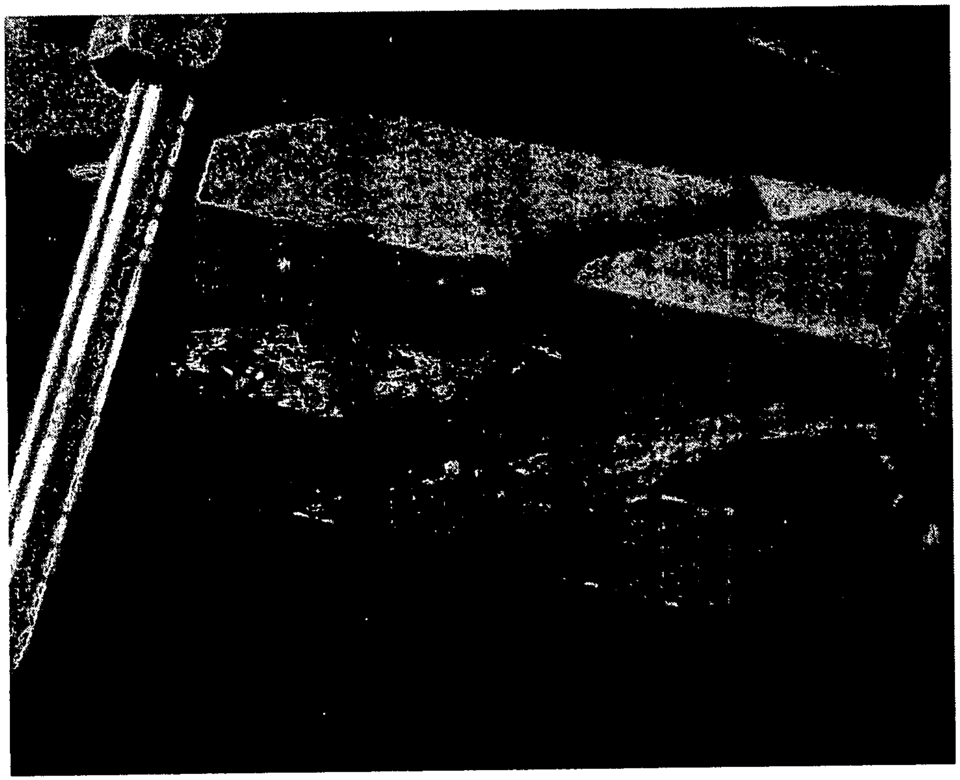
Vapor pressure development of water in dependence of temperature





Source: Hering, Modler, Grundwissen des Ingenieurs, Fachbuchverlag Leipzig, 2002

Starch extrusion according to US 4,673,438 and WO 92/15285



(click on black panel for start)

- Any attempt to extrude potatoe starch under the conditions of the above patents leads wthin very short time to blocking of the extruder.

- The cylinder must be freed from starch by heating to above 300°C.

Pilot study plant of
Leistritz GmbH Nürnberg

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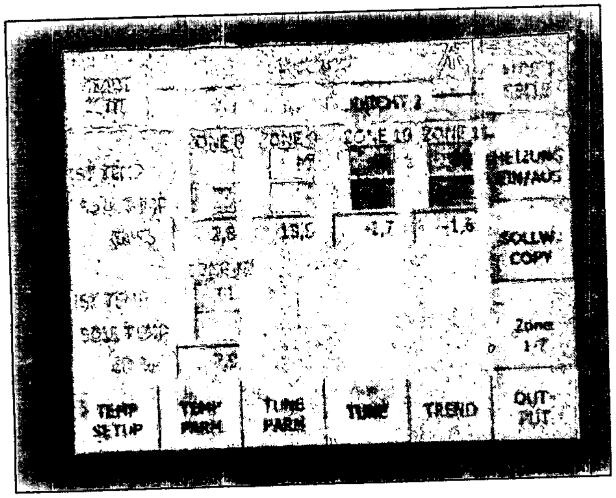
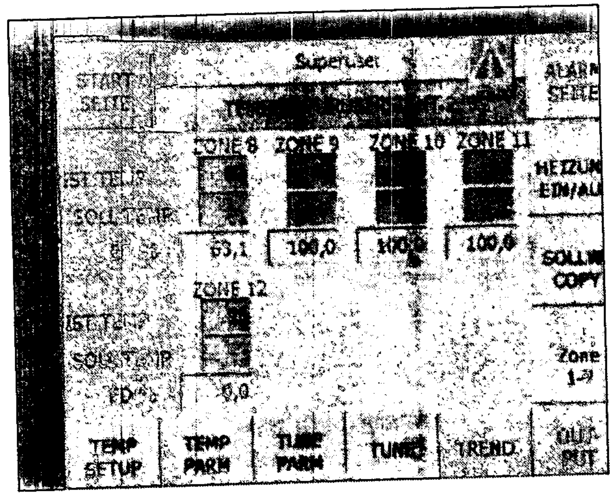
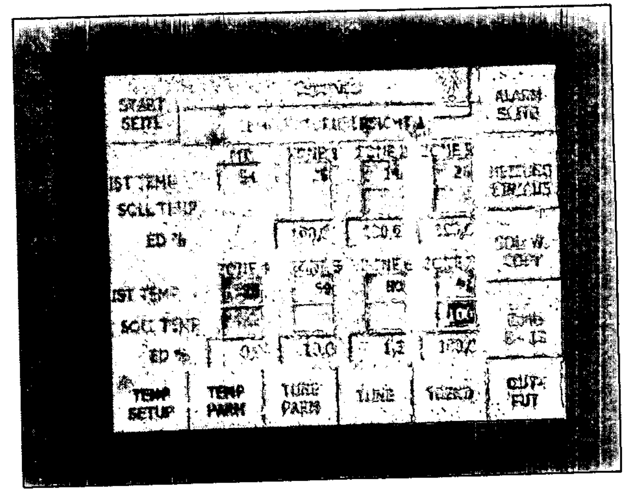
Extrusion of potatoe starch with 19 % added water (without die)







Extrusion conditions DE 199 18 325A1

Screw temperature: 80 °C

The extruded mass is plastic and free of bubbles. Extrusion proceeds without problems.

Screw temperature:

80 to 90 °C

Slow increase in screw temperature to 90 °C; the product remains extrudable.

Screw temperature:

90 to 120 °C

The extrudate becomes vitrified (amorphous) and starts popping up at approximately 100°C. At 120°C the extrudate strand breaks, the extruder blocks.

Addition of further excipients to starch

Starch extrusion according to US 4,673,438 and WO 92/15285

In order to extrude starch at higher temperatures lubricants and plasticizers must be added to the starting mixture.

Recipe 1:
Placebo

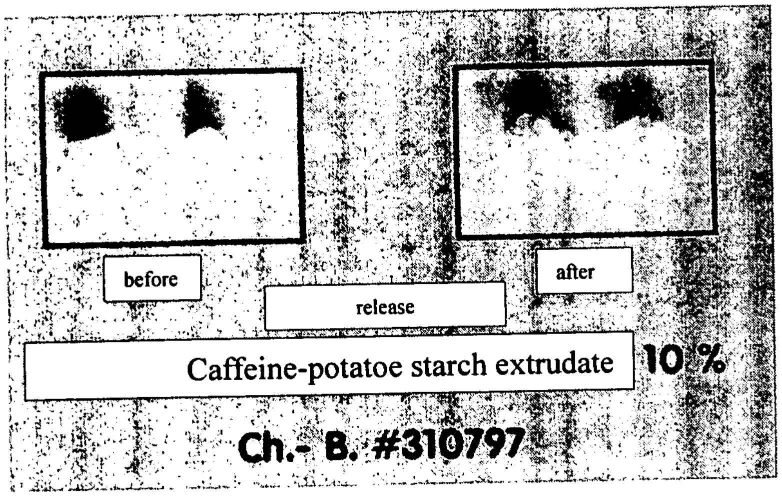
Potatoe starch	810 g
Hydrated Triglyceride*	10 g
Sojalecithine	5 g
TiO_2	5 g

Recipe 2:

Potatoe starch	810 g
Hydrated Triglyceride*	10 g
Sojalecithine	5 g
TiO_2	5 g
Tramadol * HCl	100 g

* e.g. hydrated peantut oil

Optical appearance of products according to DE 199 18 325A1, US 4,673,438 and WO 92/15285



DE 199 18 325A1

Screw temperature: 66 °C, die temperature: 98 °C

The extrudate is compact and highly dense, no air bubbles are present.

The extrudate can be transformed into a ready to use dosage form (extrudette) by cutting into desired lebghts. No further processing steps are necessary.

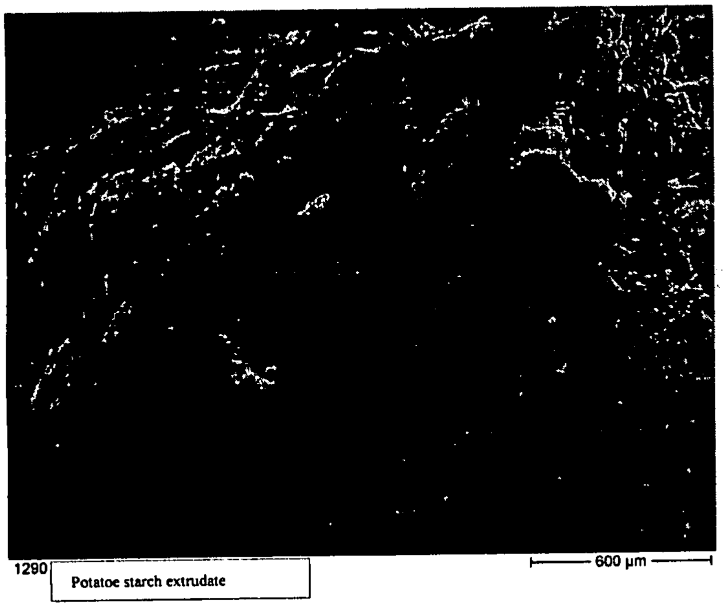
Fig.: Extrudette bevor and after release according to Pharm. Eu. 4

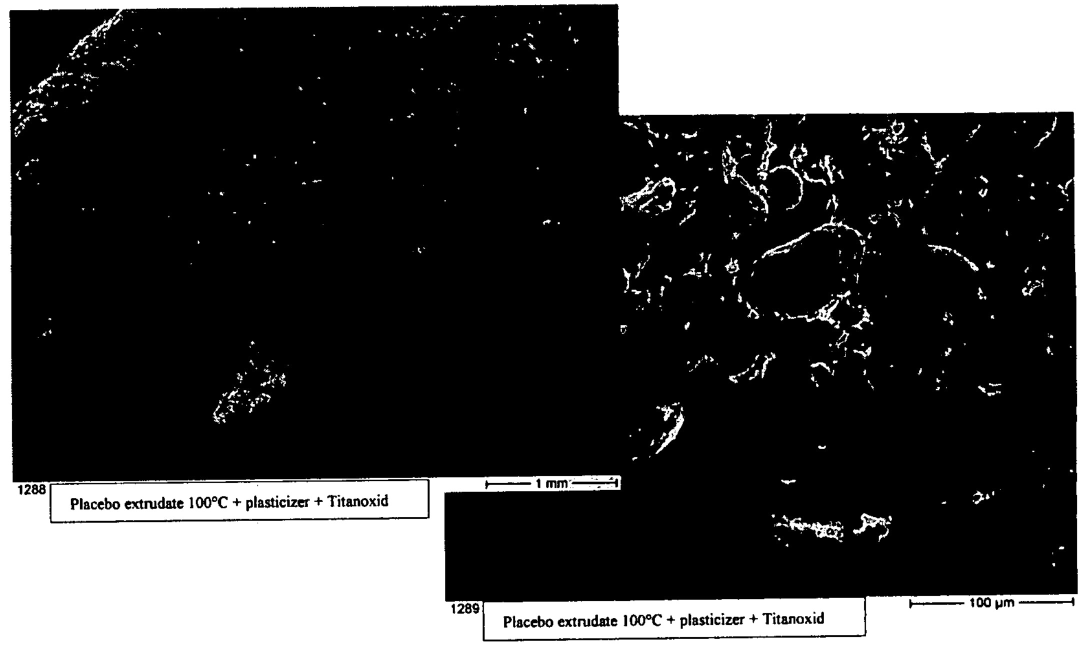
US 4,673,438 and WO 92/15285

One obtains a non-formable, coarse product with long curing time (several days).

Without further processing the extrudate is not suitable for use as a matrix in sustained release dosage forms.

SEM-pictures of different starch extrudates





Potatoe starch extrudate

Extrusion without die, screw temperature 120 °C

Since the strand popps up, the extrudate is highly disrupted. The product is not suitable as a matrix without further processing.

Potatoe starch extrudate with plasticizer and pigment addition (Recipe 1):

Extrusion without die, screw temperature 100 °C

In the extrudate one observes first voids which form by vapor evaporation. The starch is partly destructurized, but not completely amorphous.

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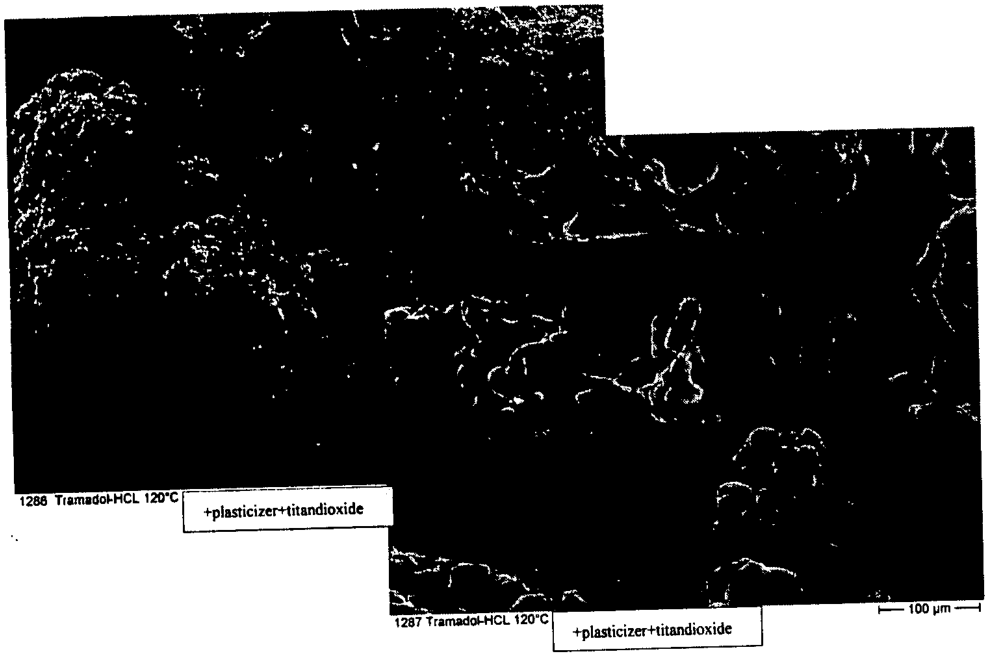
Extrudate with active agent

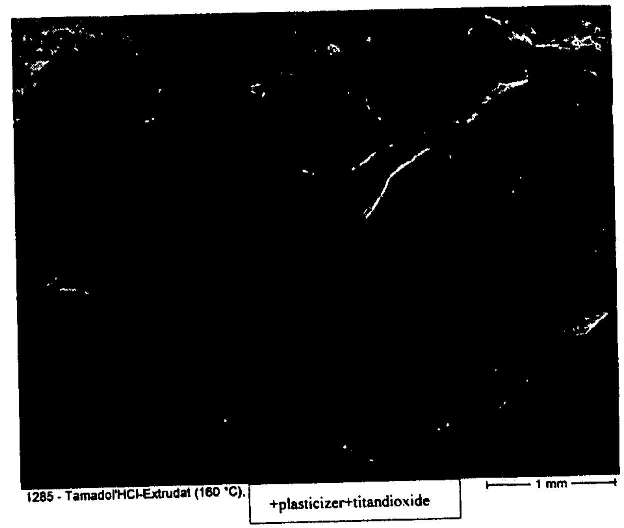
potato starch + plasticizer + pigment (Recipe 2)

REM-Abbildungen



Screw temperature 120 °C

At a screw temperature of 120°C the extrudate is already heavily disrupted by the evaporating water. The energy input is insuffoicient to vitrify the starch completely. The single starch grains are clearly visisble. The product is not suited for use as a matrix in a sustained release dosage form..



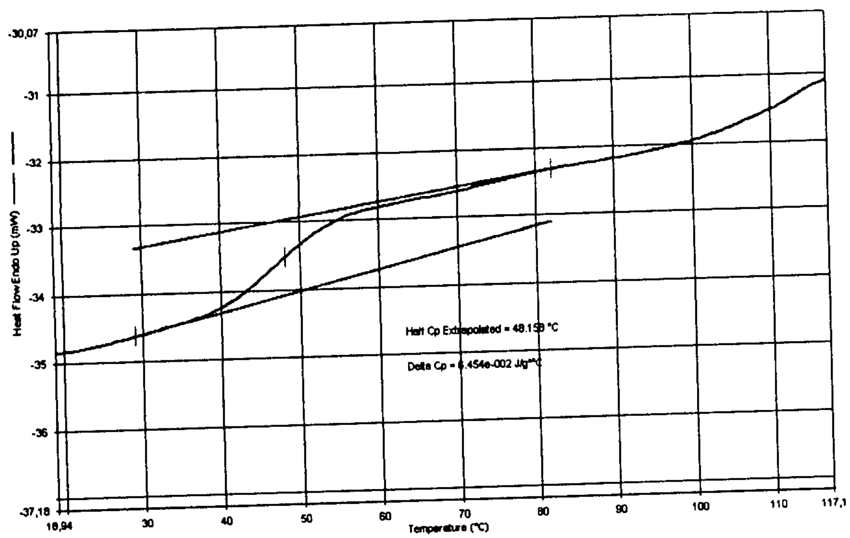
Screw temperature ca. 150 °C

At a screw temperature of approximatley 150°C an anorphous form of starch develops. The product is strongly swelled (Xerogel structure). Beacuse of the lower density, the product is not suited for use as a matrix in a sustained release dosage form.

Glas transition temperatures T_g

The glas transition temperature T_G is a measure for thermal and mechanical stress of the extruded product. The higher T_G, the less sever is the production process.

The glas transition temperature should be at least 15°C above or below the application temperature of the dosage form (37 °C), in order to ensure a constant release behaviour.



Recipe 1, screw temperature 100 °C
T_G = 48 °C

sample Extrusion conditions		T_G [°C]
Potatoe starch **DE 199 18 325A1**	screw: 82 °C die: 98 °C	106
Potatoe starch	screw: 120 °C Without die	85
Recipe 1 Placebo extrudate	screw: 100 °C Without die	48
Recipe 2 Tramadol*HCl	screw: 120 °C Without die	51
Recipe 2 Tramadol*HCl	screw: 150 °C Withou die	46

Method: PE HyperDLDK

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Starch extrusion

Experiments of 22. December 2005

Addition of further excipients to the starch

starch extrusion of US 4,673,438 and WO 92/15285

The mixture described in US 4,673,438 and WO 92/15285 (Recipe 1) was extruded under various conditions:

Recipe 1:
Placebo

Potatoe starch		810 g
Hydrated Triglycerides		10 g
Sojalecithine		5 g
TiO_2		5 g
Water:	17%	

Round die: 5 mm

221205	Temperature profil:
Exp. 1*	80 °C – 80 °C – 80 °C
Exp. 2	80 °C – 120 °C – 120 °C
Exp. 3	80 °C – 140 °C – 120 °C
Exp. 4**	80 °C – 160 °C – 120 °C

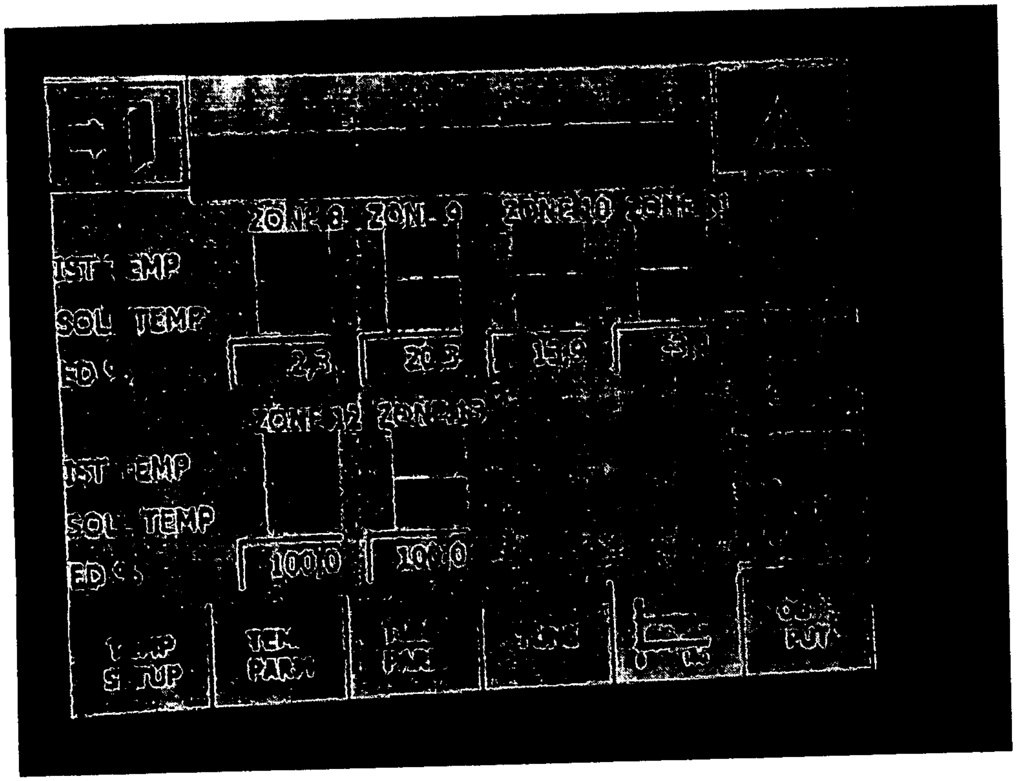
Screw speed: 75 U/Min.
Residence time (Exp 4): 75 s

* Extrusion conditions according to ***DE 199 18 325A1***

** Extrusion conditions according to ***US 4,673,438***

Starch extrusion: Exp. 1 (221205)

Temperature profil: 80 °C – 80 °C – 80 °C



- Extrusion proceeds without problems
- The product is partially popped.

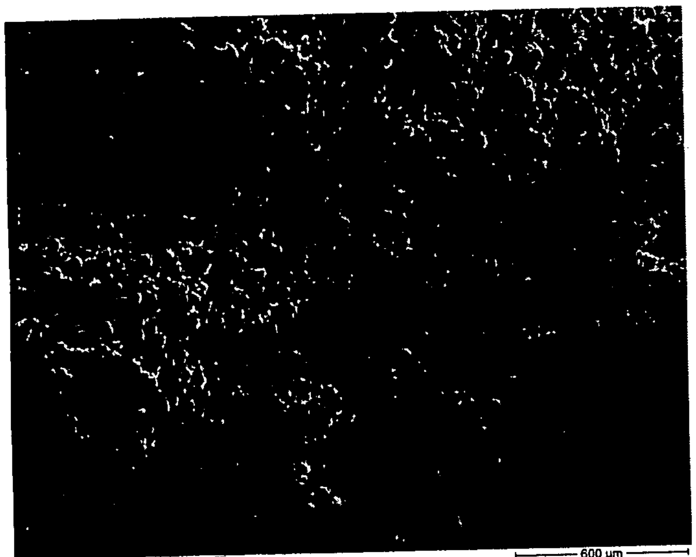
Extrusions according to

DE 199 18 325A1

Starch extrusion: Exp. 1 (221205)

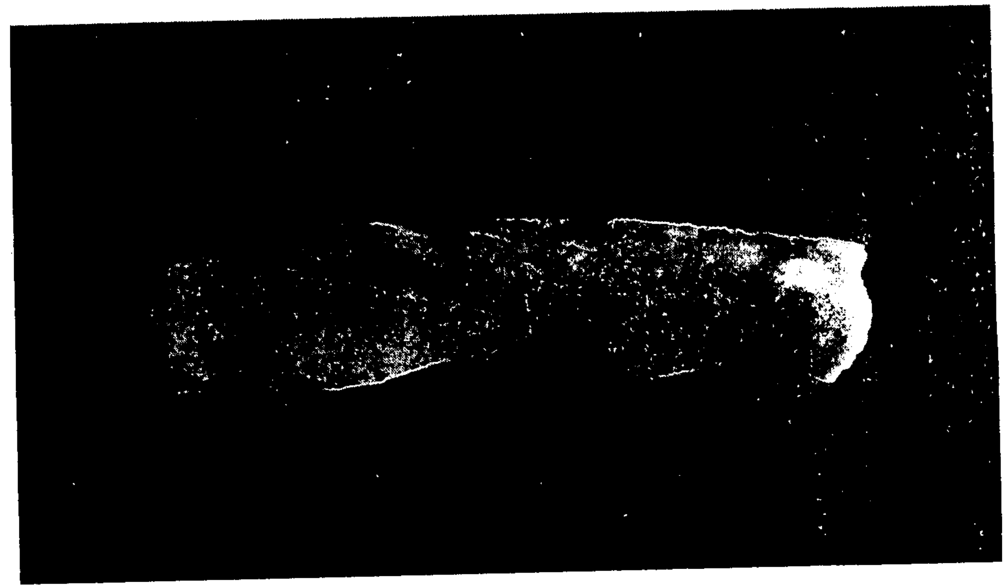
Temperature profile: 80 °C – 80 °C – 80 °C

Product properties:



Potatoe starch mixture, 80°C

Fracture surface



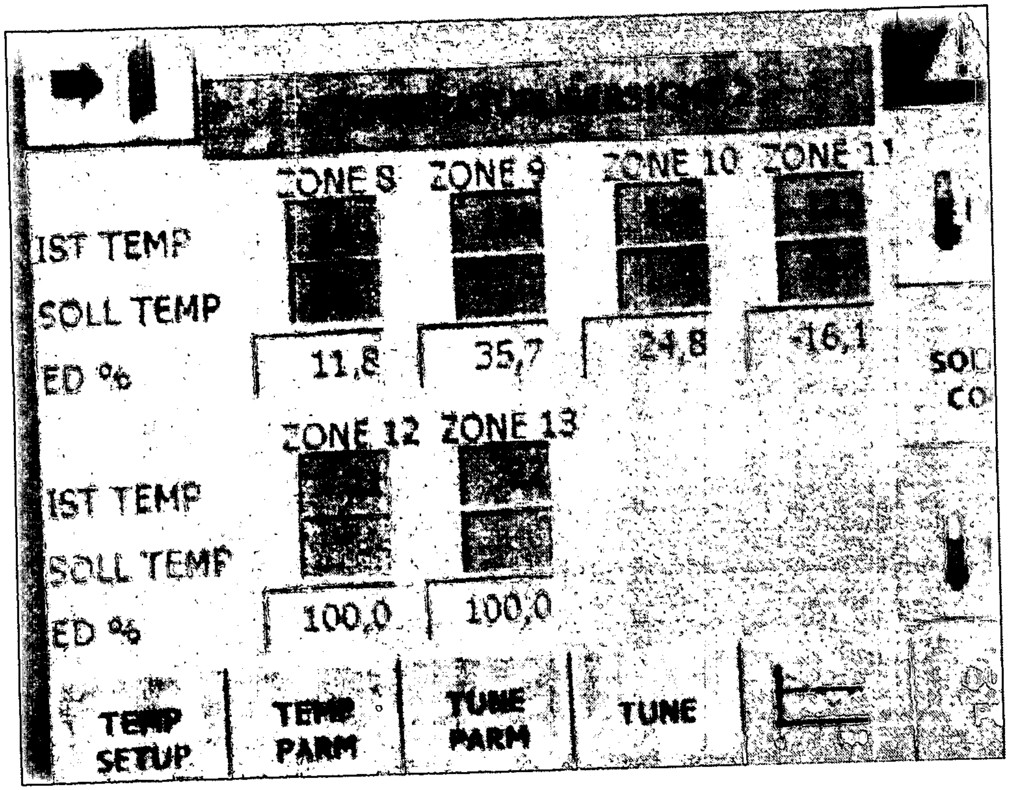
Product strand with multiple, non-vitrified starch grains;

Glas transition temperature: 85 °C

(Hyper-DSC$^{Wz.}$)

Starch extrusion: Exp. 2 (221205)

Temperature profile: 80 °C – 120 °C – 120 °C



- Popped Product;
- Clear strand breakage;
- Extrudate is not suitable as a dosage form.

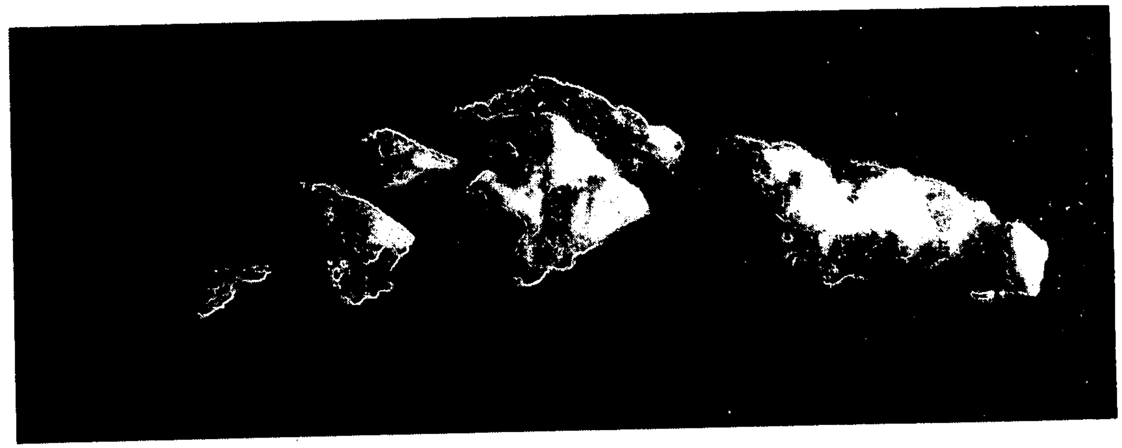
Starch extrusion: Exp. 2 (221205)

Temperature profile: 80 °C – 120 °C – 120 °C

Product properties:

Placebo + plasticizer + TiO2

Fracture surface



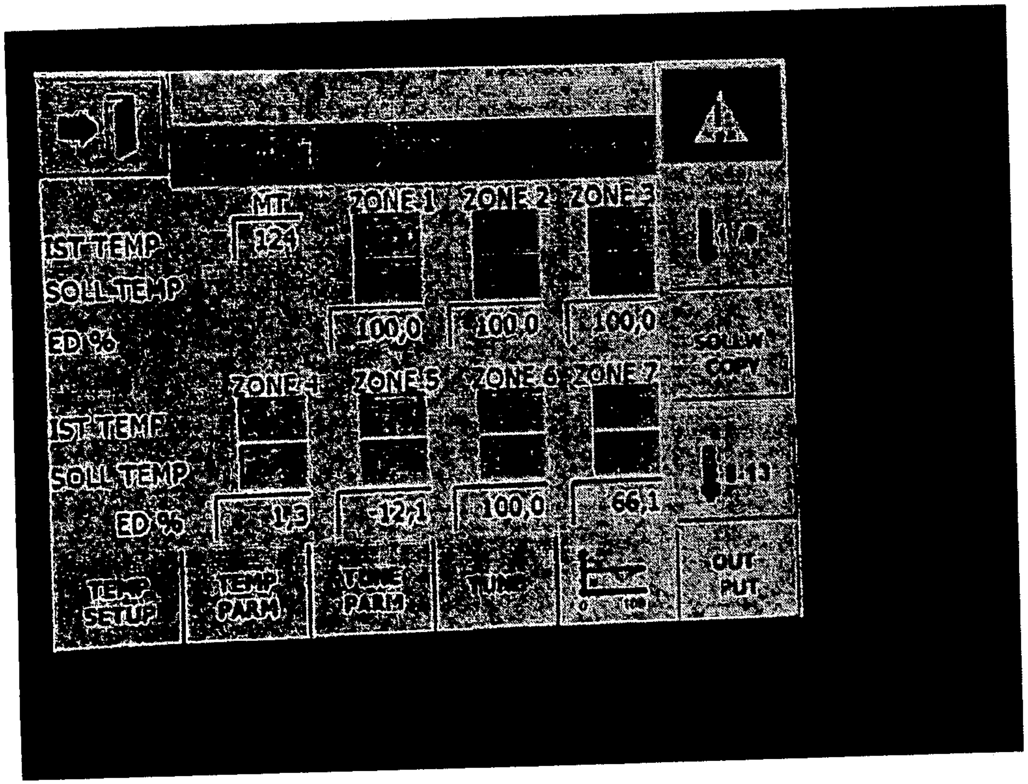
Heavily disrupted extrudate, not suitable as dosage form.

Glas transition temperature: 77 °C

(Hyper-DSC$^{Wz.}$)

Starch extrusion: Exp.3 (221205)

Temperature profile: 80 °C – 140 °C – 120 °C

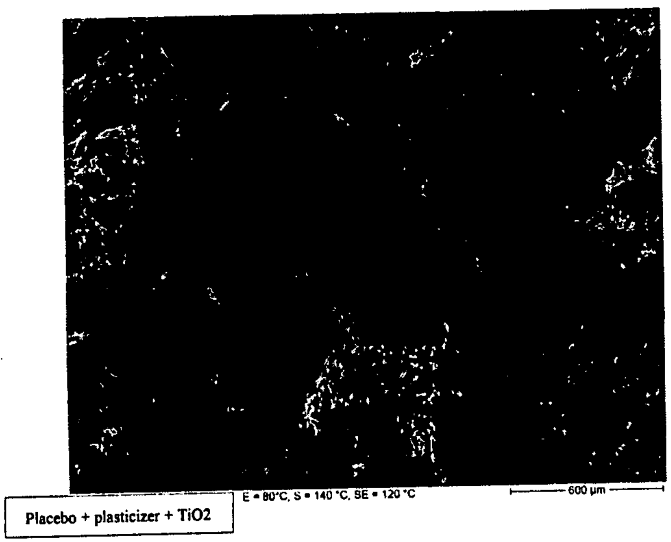


- Non-controllable extrusion process;
- Foamed product;
- The incorporated water exits the die abruptly due to the high vapor pressure

Starch extrusion: Exp. 3 (221205)

Temperature profile: 80 °C – 140 °C – 120 °C

Product properties:



Fracture surface

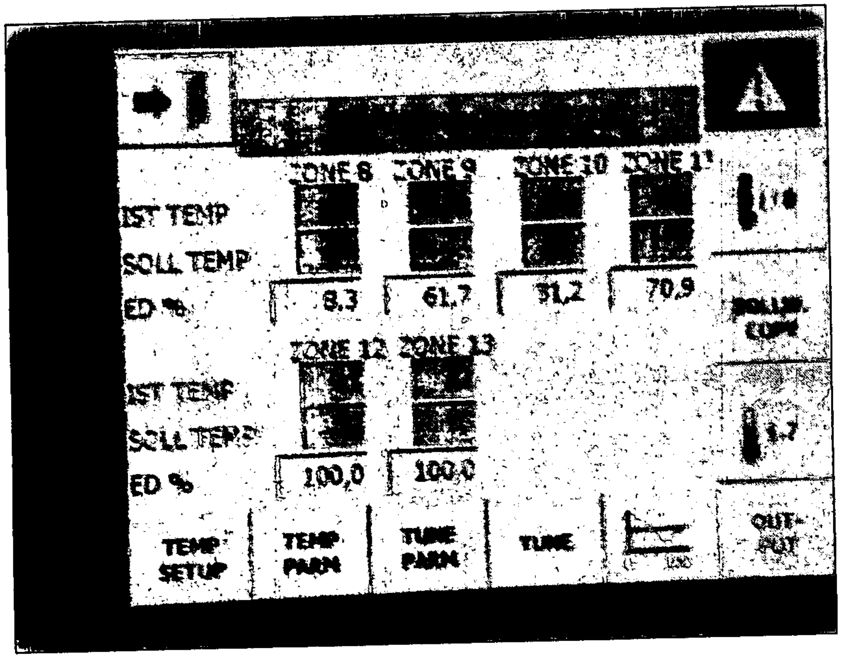
Foamed product, not suitable as mono block dosage form

Glas transition temperature: 75 °C

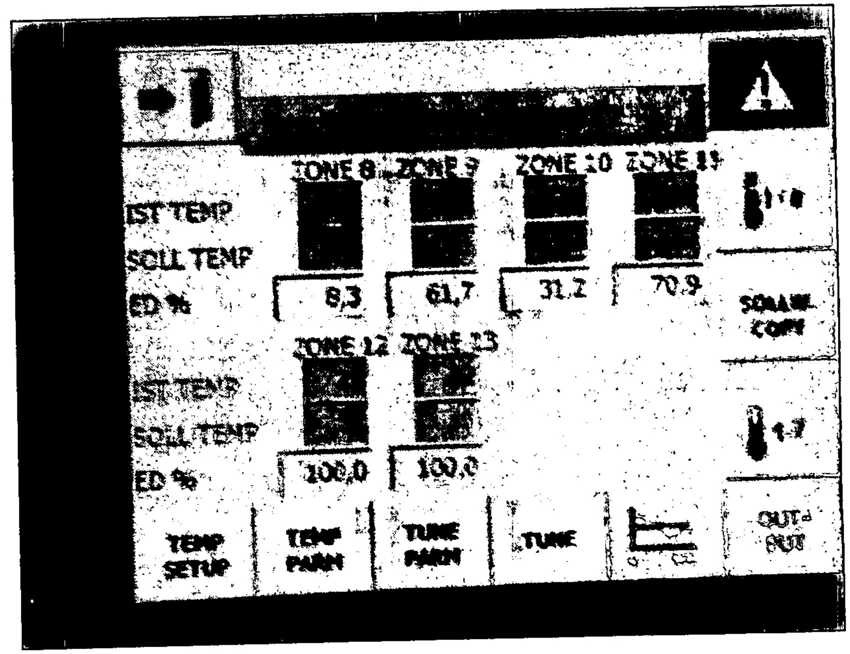
(Hyper-DSC$^{Wz.}$)

Starch extrusion: Exp. 4 (221205)

Temperature profile: 80 °C – 160 °C – 120 °C



When starting the extruder, water vapor exits the die with high pressure.



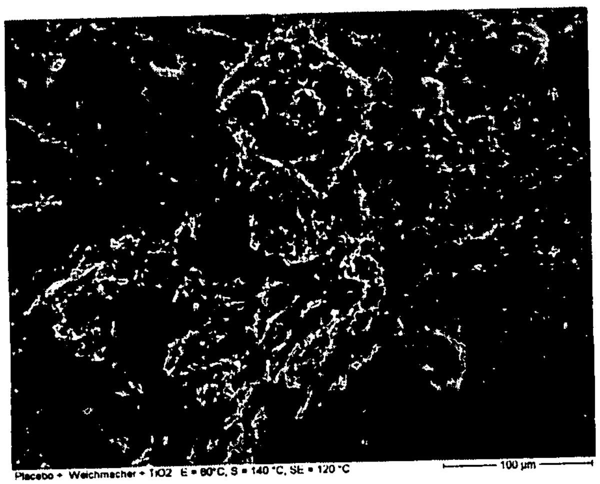
The extrusion process is not controllable. The foam that abruptly exits the die contains charred components due to the high temperature

Extrusion conditions according to *US 4,673,438*

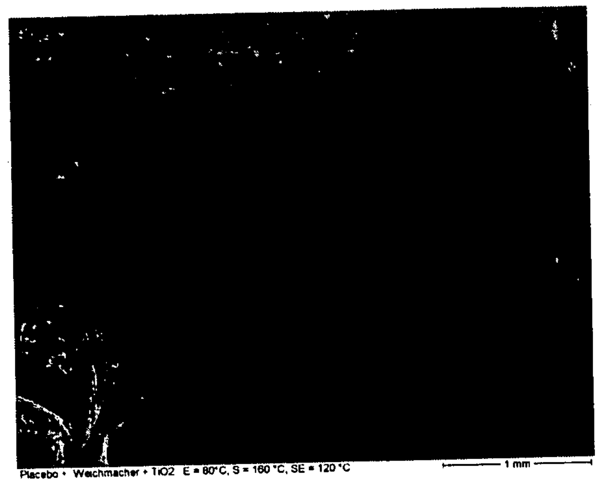
Starch extrusion: Exp. 4 (221205)

Temperature profile: 80 °C – 160 °C – 120 °C

Product properties:



Fracture surface



Fracture surface

Dry foam: The bubble walls are highly porous, the product is not suitable as a mono block dosage form.

Glas transition temperature:67 °C (Hyper-DSC[Wz.])

Extrusions conditions according to *US 4,673,438*

Conclusions

Extrusion processes as described in ***DE 199 18 325A1*** and ***09/980 727*** or. ***PCT/EP00/03612*** lead to different products.

DE 199 18 325A1

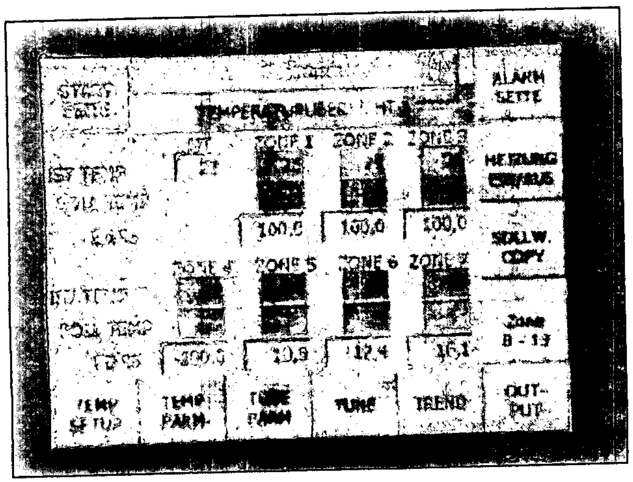
- production of mono block sustained relase dosage forms and granules is possible.
- Comparatively low thermal stress for the starting products.
- »One excipient concept« is possible.
- Führt auf direktem Weg zur fertigen Arzneiform.

US 4,673,438 and WO 92/15285

- high thermal stress for starting substance
- TG in application window leads to release behaviour that is hard to calculate
- Extrusion – if at all – is possible only with additional excipients such as lubricants and plasticizers
- Extensive processing steps are necessary to obtain administratable dosage form
- Production of non-popped products is not possible.
- High bulk volume means voluminous dosage forms

Addition of further excipients to the starch

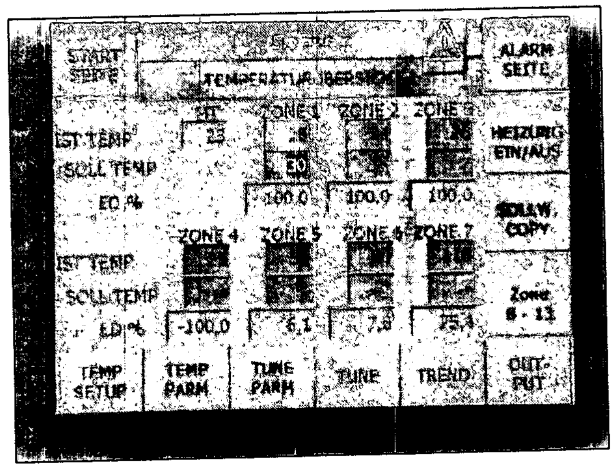
Starch extrusion according to US 4,673,438 and WO 92/15285



Extrusion at 80 – 100 °C

(Recipe 1)

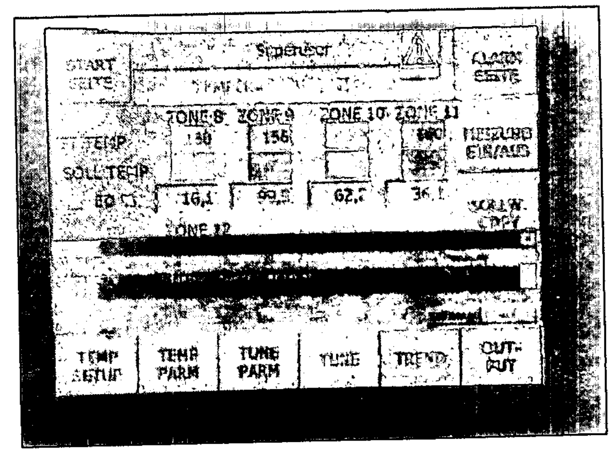
The mixture can be extruded without problems.



Extrusion at 100 – 130 °C

(Recipe 2
with 10 % Tramadol*HCl

The mixture can be well extruded. As a product one obtains the flakes that are typical for this temperature. Partially, popping up occurs.



Extrusion at 160 °C

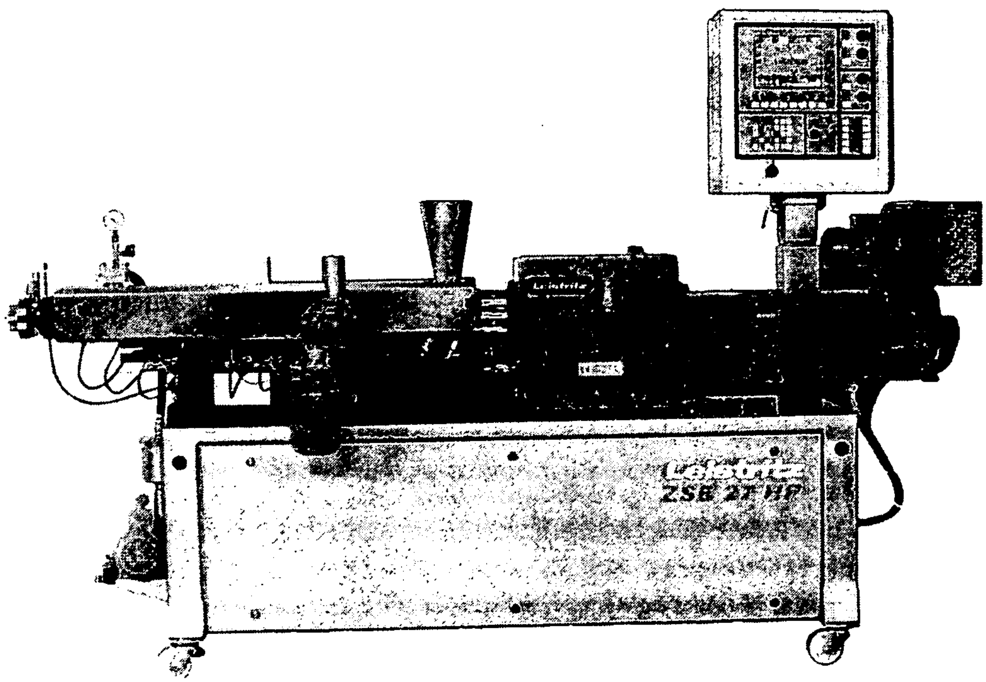
(Recipe 2
With 10 % Tramadol*HCl

The mixture can be extruded; however, it popps up significantly. The prdoct is highly porous. When trying to extrude the mixture with the die plate, the extruder blocks.

Experimental Report

1. Extruder:

A Leistritz ZSE 27 HP 32 D extruder was used. It is a co-rotating twin screw extruder:



2. Extruded Mixture

The following mixture was used in the extruder experiments (see also Experiment 1 of WO 92/15285):

potato starch	810 g
hydrogenated triglyceride	10 g
soya lecithin	5 g
TiO_2	5 g
Water	17.00 %

3. Experiments

The above mixture was extruded under 4 different parameter conditions (see below Table 1):

	Barrel Temperature Profil
Experiment 1	80°C – 80°C – 80°C
Experiment 2	80°C – 120°C – 120°C
Experiment 3	80°C – 140°C – 140°C
Experiment 4	80°C – 160°C – 120°C

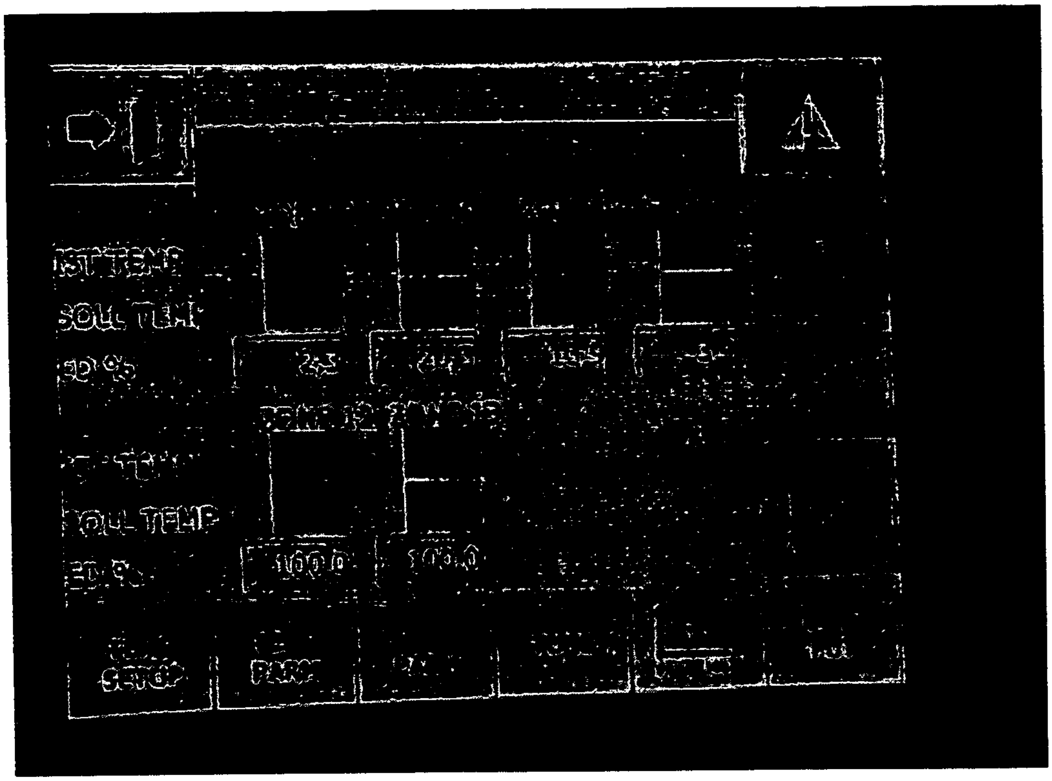
The screw speed was 75 rpm/min.
A round noozle of 5 mm diameter was used.

- The temperature profile of Experiment 1 conforms with the teaching of the present invention.
- The temperature profiles of Experiments 2 to 4 stepwise approach the conditions as set forth in Experiment 1of WO 92/15285 in combination with US 4,673,438 (see page 28, lines 5 to 30 of WO 92/15285).

4. Results

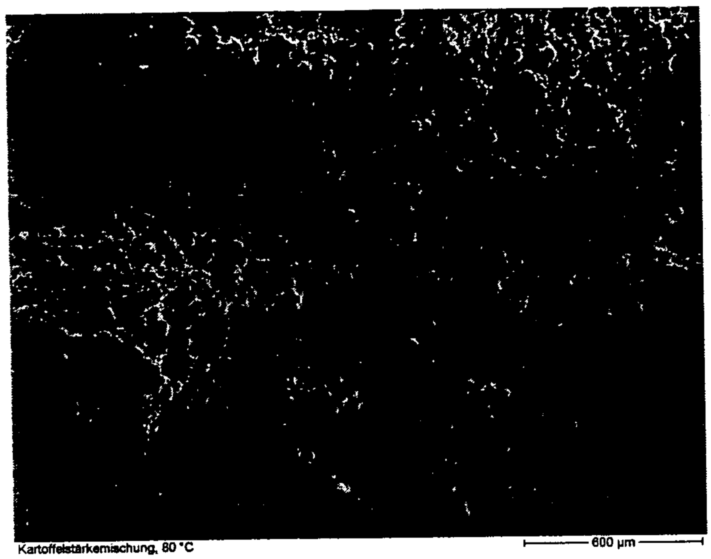
4.1 Experiment 1

Online monitor shot:



Product appearance:

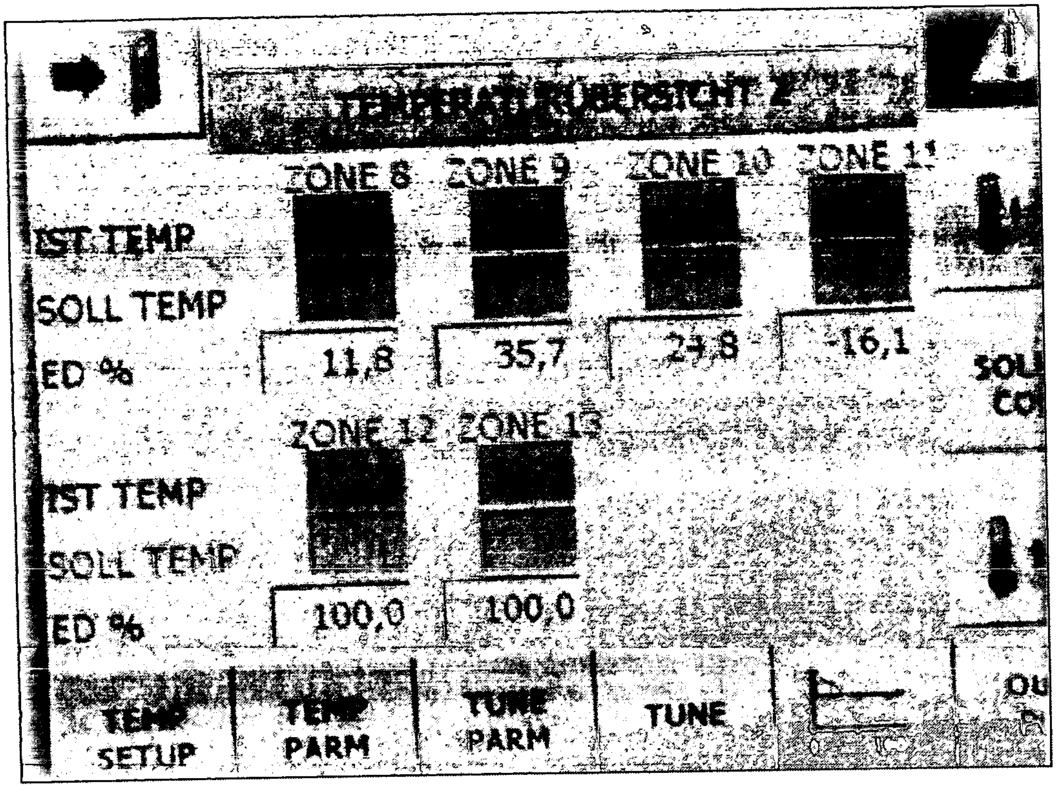
Electron microscopy picture of fracture surface:



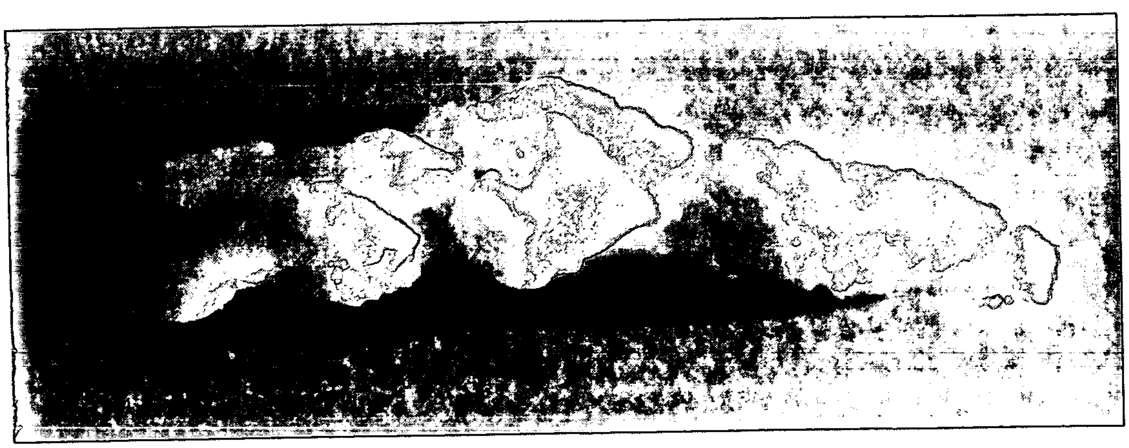
The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 85°C.

4.2 Experiment 2

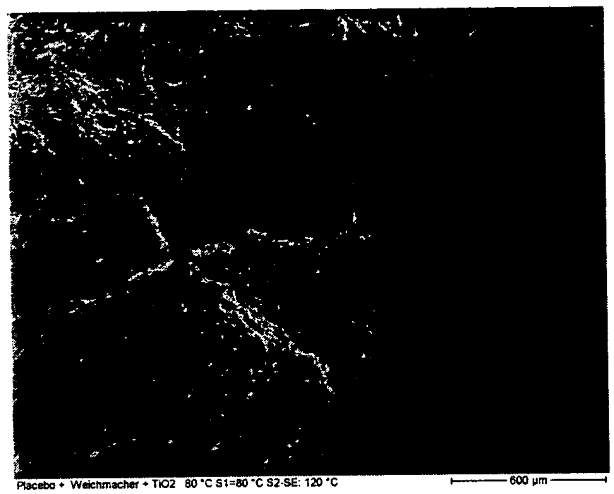
Online monitor shot:



Product appearance:



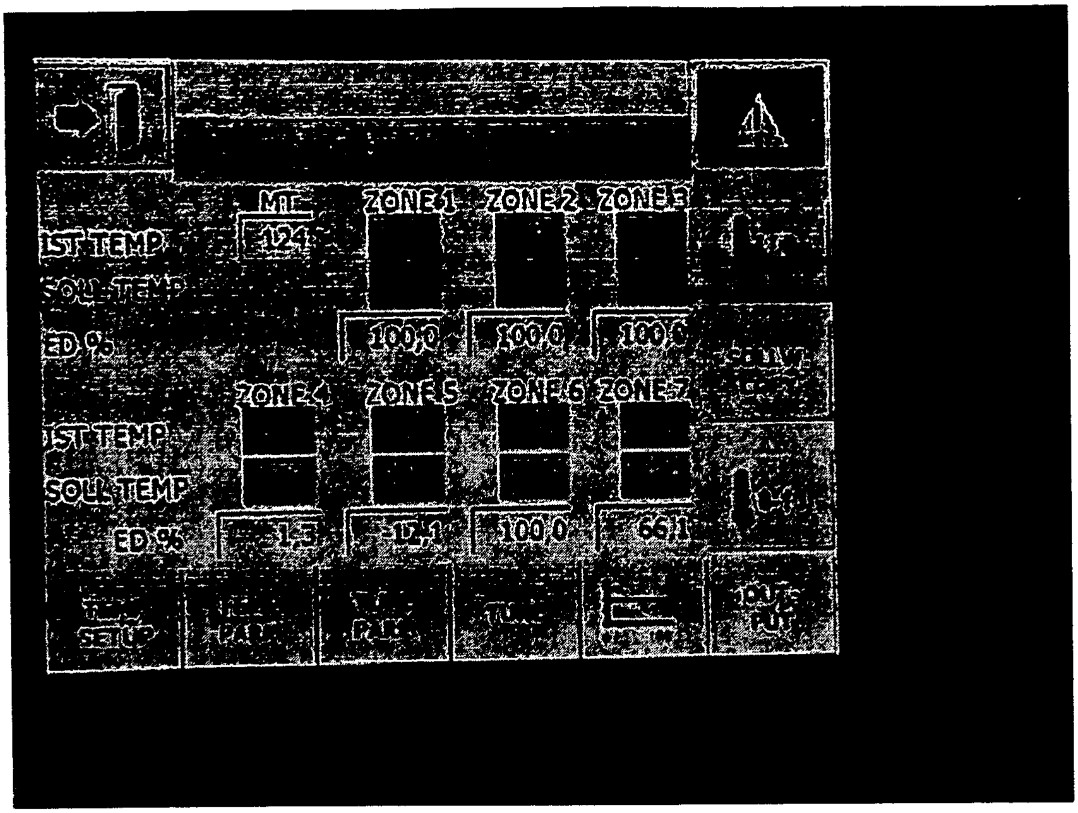
Electron microscopy picture of fracture surface:



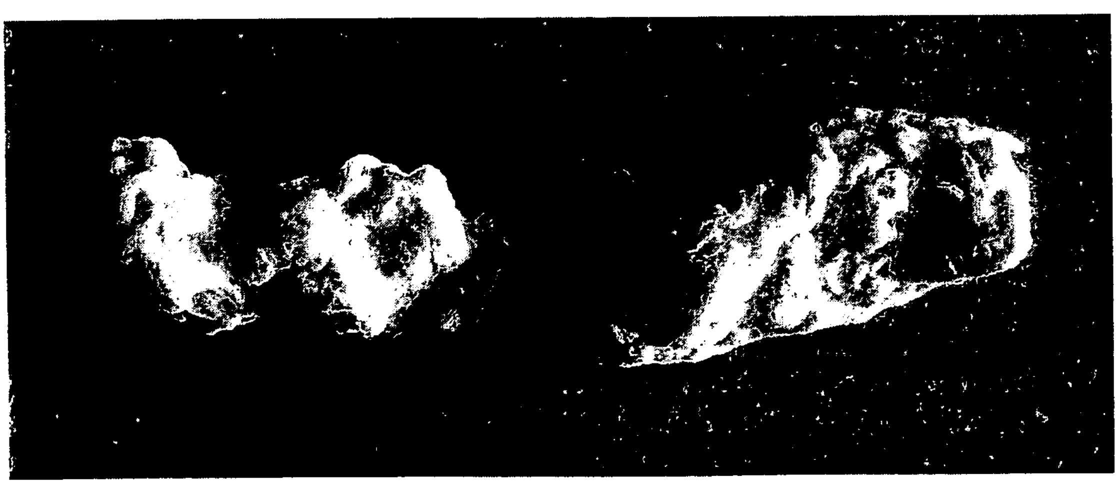
The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 77°C.

4.3 Experiment 3

Online monitor shot:



Product appearance:



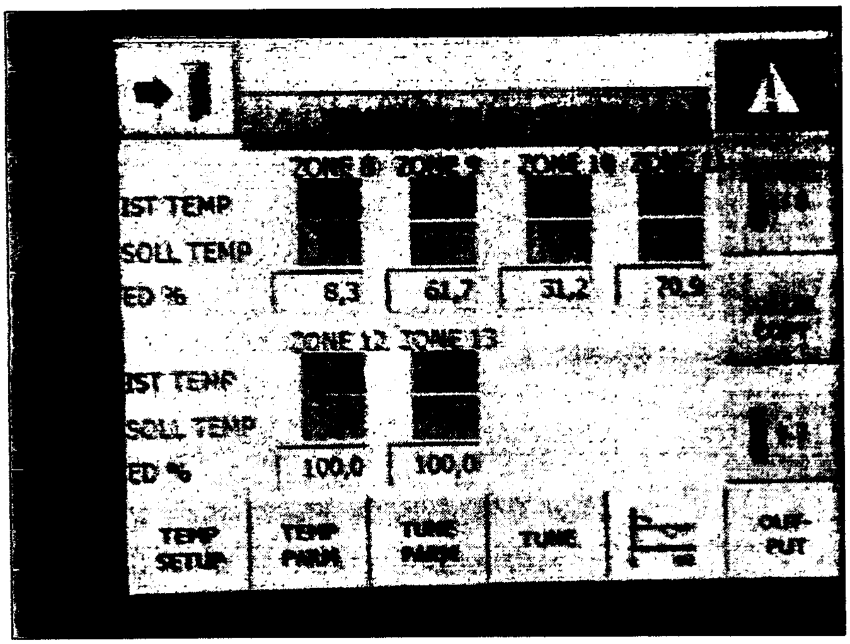
Electron microscopy picture of fracture surface:

The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 75°C.

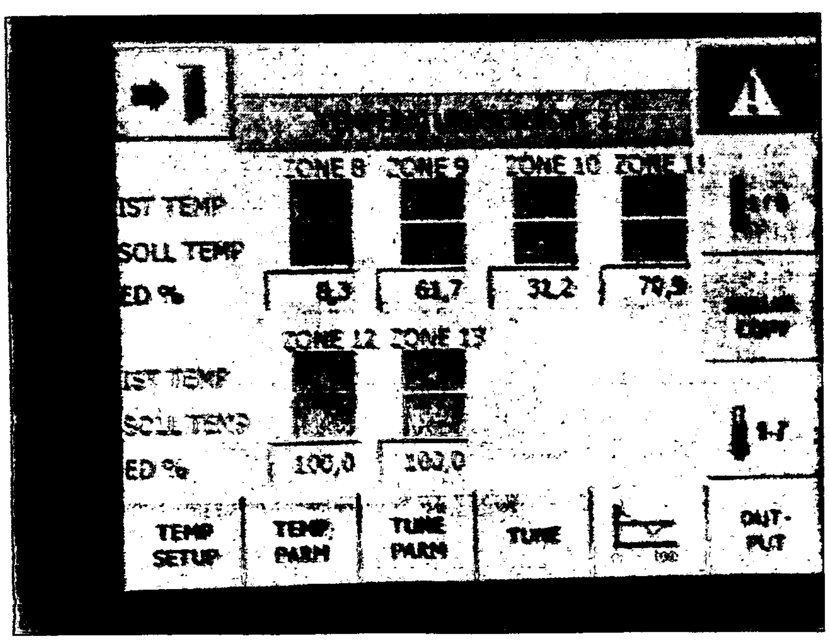
4.4 Experiment 4

Online monitor shots:

When starting the extruder, water vapor leaves the noozle under high pressure:



The extrusion process can not be controlled. A foam is formed.



Product appearance:

Electron microscopy picture of fracture surface:

The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 67°C.